Induced Pluripotent Stem Cells from Patients with Huntington's Disease Show CAG-Repeat-Expansion-Associated Phenotypes.

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Public Summary:
Huntington's disease (HD) is an inherited brain disorder that involves the loss of neurons in specific regions of the brain. Symptoms include changes in behavior and movement deficits, and ultimately result in death. The disease is caused by an expanded stretch of repeating CAG nucleotides in the HD gene, which codes for an expanded stretch of glutamate residues (poly-Q) within the Huntingtin (HTT) protein. The presence of more than 40 CAGs invariably causes disease within a normal lifespan, and longer repeats predict younger disease onset. Although the mutation causing HD is known, our understanding of the pathogenesis is incomplete, and there is no treatment to delay the onset or slow the progression of HD. Novel techniques to generate induced pluripotent stem cell (iPSC) lines – which have the ability to differentiate into any cell type – directly from patient samples (e.g. skin cells) has led to the development of numerous “disease in a dish” models. Such models have the capacity to mimic aspects of human disease, and improve upon previous non-human models, which ultimately translates into novel therapies. They can also serve as powerful tools for studying disease mechanisms in a human context. Here, The HD iPSC Consortium reports the generation and characterization of 14 iPSC lines from HD patients and controls. We utilized this common set of lines to test whether various defects exist within HD lines. Analysis of genes expressed revealed mutation-dependent patterns that distinguish patient lines from controls, and early onset (longer CAG repeat lengths) versus later onset (medium CAG repeat lengths). HD neural cells derived from the iPS cells showed disease-associated deficits in the ability to retain normal functional characteristics, including electrical activity, energy production, and cell adhesion. Survival of HD cells was also decreased compared to control, as observed in studies assessing the risk of cell death during development into mature neurons. In addition, exposure to cellular stressors and withdrawal of important growth factors caused more detrimental effects in HD lines compared to controls. Importantly, cells with longer CAG repeat lengths were most vulnerable as assessed using the range of assays mentioned above, and was established and confirmed across consortium laboratories in order to eliminate the possibility of non-HD-associated effects. Taken together, the findings suggest that repeat mutation-dependent deficits can be measured using this human iPSC model. The HD iPSC collection represents a unique and well-characterized resource to elucidate disease mechanisms in HD and provides a valuable human stem cell platform for screening new candidate therapeutics.

Scientific Abstract:
Huntington's disease (HD) is an inherited neurodegenerative disorder caused by an expanded stretch of CAG trinucleotide repeats that results in neuronal dysfunction and death. Here, The HD Consortium reports the generation and characterization of 14 induced pluripotent stem cell (iPSC) lines from HD patients and controls. Microarray profiling revealed CAG-repeat-expansion-associated gene expression patterns that distinguish patient lines from controls, and early onset versus late onset HD. Differentiated HD neural cells showed disease-associated changes in electrophysiology, metabolism, cell adhesion, and ultimately cell death for lines with both medium and longer CAG repeat expansions. The longer repeat lines were however the most vulnerable to cellular stressors and BDNF withdrawal, as assessed using a range of assays across consortium laboratories. The HD iPSC collection represents a unique and well-characterized resource to elucidate disease mechanisms in HD and provides a human stem cell platform for screening new candidate therapeutics.

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